## REMARKS

In an Office Action dated November 14, 2006, pending claims 1-18 were rejected. This document is submitted in response to said Office Action.

Double Patenting

The Examiner has rejected claims 1-18 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 9-14 of US Patent No. 6,713,616 and claims 2-4 of US Patent No. 6,346,611. The Examiner asserts that although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are directed to methods of using the compounds claimed in each of the patents. The Examiner reasons that the patentability of the patented claims is considered in view of the ability to make and use the compound, thus the uses of these compounds recited in the instant claims would have been obvious in view of the patentability of the compounds.

The M.P.E.P. provides that the doctrine of double patenting seeks to avoid unjustly extending patent rights at the expense of the public; therefore, the focus of any double patenting analysis necessarily is on the claims in the multiple patents or patent applications involved in the analysis. (M.P.E.P. § 804). With respect to obviousness-type double patenting the M.P.E.P. provides in relevant part:

> These factual inquiries are summarized as follows:
>
> (A) Determine the scope and content of a patent claim relative to a claim in the application at issue;
>
> (B) Determine the differences between the scope and content of the patent claim as determined in (A) and the claim in the application at issue;
>
> (C) Determine the level of ordinary skill in the pertinent art; and
>
> (D) Evaluate any objective indicia of nonobviousness.
>
> The conclusion of obviousness-type double patenting is made in light of these factual determinations.

> Any obviousness-type double patenting rejection should make clear:
>
> (A) The differences between the inventions defined by the conflicting claims - a claim in the patent compared to a claim in the application; and
>
> (B) The reasons why a person of ordinary skill in the art would conclude that the invention defined in the claim at issue is anticipated by, or would have been an obvious variation of, the invention defined in a claim in the patent.
>
> When considering whether the invention defined in a claim of an application would have been an obvious variation of the invention defined in the claim of a patent, the disclosure of the patent may not be used as prior art. *General Foods Corp. v. Studiengesellschaft Kohle mbH*, 972 F.2d 1272, 1279, 23 USPQ2d 1839, 1846 (Fed. Cir. 1992).

M.P.E.P.§804(II)(B)(1).

Applicants submit that Claims 1-18, as amended, which are directed to a method for inhibiting a transforming growth factor β2 (TGFβ2), a method for targeting a nucleic acid ligand of TGFβ2 to a site in a patient, and a method for treating TGFβ2-mediated pathological conditions are not obvious variations of claims 9-14 of US Patent No. 6,713,616 and claims 2-4 of US Patent No. 6,346,611. Although the patentability of the patented claims is considered in view of the ability to make and use the compound under 35 U.S.C. §101, the comparison in an obviousness-type double patenting rejection is appropriate between the issued claims, and whether or not what is claimed in the application is an obvious variation of what was claimed in the issued patent. In the present case, it is not obvious that producing the compounds claimed in claims 9-14 of US Patent No. 6,713,616 and claims 2-4 of US Patent No. 6,346,611, will provide for a method for inhibiting a transforming growth factor β2 (TGFβ2), a method for targeting a nucleic acid ligand of TGFβ2 to a site in a patient, and a method for treating TGFβ2-mediated pathological conditions. These methods are specifically claimed because a ligand to TGFβ2 may have many uses.

The Examiner asserts that the Applicants above arguments are not persuasive. The Examiner states that,

> The claimed methods are an obvious variation of the patent claims because the patent claims are directed to TGFβ2 nucleic acid ligands and the disclosure of each of the patents specifically contemplates at column 1, 'This invention also includes high affinity nucleic acid inhibitors of

> TGFβ2. The oligonucleotide ligands of the present invention are useful in any process in which binding to TGFβ2 is required. This includes, but is not limited to, their use as pharmaceuticals, diagnostics, imaging agents, and immunohistochemical reagents.' While a ligand to TGFβ2 might have many uses, it would be obvious to one of ordinary skill in the art to use the ligands for the purposes specifically contemplated in the specification of each of the patents.

Office Action at 2-3. The Examiner relies on the specification of the prior application in order to prove obviousness, not the issued claims themselves. The requirement from the MPEP is that the issued claims are compared to the pending claims, as opposed to comparing the specification of the prior patent to the claims of the present application. The claims of the present application are not obvious in view of the issued claims of patents 6,713,616 and 6,346,611. Reconsideration is respectfully requested.

The Rejection under 35 U.S.C. § 112, first paragraph—Enablement Requirement

The Examiner has rejected claims 1-18 under 35 U.S.C. § 112, first paragraph, for lack of enablement. While the Examiner admits that the specification is enabling for use of a nucleic acid ligand to TGFβ2 to inhibit TGFβ2-mediated proliferation of cultured cells, the Examiner argues that the specification does not provide enablement for targeting a nucleic acid to a site in a patient, inhibition of TGFβ2 *in vivo* or treatment of a pathological condition mediated by TGFβ2 *in vivo* in any organism using a nucleic acid ligand to TGFβ2.

The first paragraph of § 112 requires that a patent application be written so as to "enable any person skilled in the art to which it pertains . . . to make and use the same." A specification is presumed to be enabling absent "a reason to doubt the objective truth of the statements contained therein." *In re Marzocchi*, 169 USPQ 367, 369 (C.C.P.A 1971). Further, a specification "may be enabling even though some experimentation is necessary," *United States v. Teletronics, Inc.*, 857 F.2d 778, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988), as long as the amount of experimentation required is not "undue experimentation." *In re Wands*, 858 F. 2d 731, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). The test is whether the specification "provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands*, 858 F. 2d 731, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The Examiner argues that while the specification is enabling for the use of a nucleic acid ligand to TGFβ2 to inhibit TGFβ2-mediated proliferation of cultured cells, the specification does not reasonably provide enablement for targeting a nucleic acid ligand to a site in a patient, inhibiting TGFβ2 *in vivo* or treating a pathological condition mediated by TGFβ2 *in vivo* in any organism using a nucleic acid ligand to TGFβ2.

The Examiner agrees that the specification does provide guidance regarding the pharmacokinetics of representative nucleic acid ligands in rats, teachings of the isolation of nucleic acid ligands that bind human TGFβ2, teachings of therapeutic compositions and guidance on post-SELEX modifications that improve in vivo stability. However, the Examiner cites Opalinska et al., stating that this reference illustrates the issues of delivery recognized in the art. Applicants assert that the delivery of nucleic acid ligands *in vivo* is not addressed in Opalinska et al., and that this reference does not describe the state of the art with regard to nucleic acid ligands.

In the abstract, Opalinska et al., specifically states, "This article reviews different strategies for modulating gene expression, and discusses the successes and problems that are associated with this type of therapy." Opalinska at 503. Further, the article states,

> Nucleic-acid-mediated gene silencing has been used with great success in the laboratory, and this strategy has also generated some encouraging results in the clinic. Nevertheless, it is widely appreciated that the ability of nucleic-acid molecules to modify gene expression in vivo is quite variable, and therefore wanting in terms of reliability. Several issues have been implicated as a root cause of this problem, including molecule delivery to targeted cells and specific compartments within cells, and identification of sequence that is accessible to hybridization in the genomic DNA or RA. Intuitively, DNA accessibility is limited by compaction of nuclear material and transcription activity of the gene target.

Opalinska at 511.

Thus Opalinska is limited to discussing the efficacy of nucleic acid gene therapy. Nucleic acid ligands are not designed to work in vivo in a similar manner to that of nucleic acids for gene targeting. The issues associated with the therapies are completely different. Nucleic acid ligands are not naturally occurring substances and they are not designed to alter gene expression. Instead they are non-naturally occurring molecules that are designed to modulate the activity of proteins. As the Examiner has not proffered evidence to the contrary with regard to

nucleic acid ligands, under the standard of *In re Marzocchi,* the specification is presumed to be enabling. *In re Marzocchi*, 169 USPQ 367, 369 (C.C.P.A 1971). Reconsideration is respectfully requested.

The Rejection under 35 U.S.C. § 103, Obviousness

The Examiner has rejected Claims 1 and 3-5 as being unpatentable over Gold et al., (US 5,270,163) in view of Tullis (WO 88/09810) and Shah et al. (Journal of Cell Science 1995). The Examiner bears the burden of establishing a prima facie case of obviousness under 35 U.S.C. § 103. In determining obviousness, one must focus on Applicant's invention as a whole. Symbol Technologies Inc. v. Opticon Inc., 19 U.S.P.Q.2d 1241, 1246 (Fed. Cir. 1991). The primary inquiry is:

> whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have had a reasonable likelihood of success . . . . Both the suggestion and the expectation of success must be found in the prior art, not in the applicant's disclosure.

In re Dow Chemical, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988). According to the MPEP § 2143, "to establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Third, the prior art references (or references when combined) must teach or suggest all the claim limitations." Obviousness cannot be established by combining teachings in the prior art, absent some teaching or suggestion in the prior art that the combination be made (*In re Stencel* 828 F. 2d 751, 4 USPQ2d 1071 (Fed. Cir. 1987); *In re Newell* 891 F. 2d 899, 13 USPQ2d 1248 (Fed. Cir. 1989)).

The Examiner asserts that Gold et al. teach a method of identifying nucleic acid ligands, that Tullis teaches nucleic acid conjugates comprising an antisense conjugated to a solubility-modifying moiety, and that Shah et al. teach that TGFβ2 is one TGFβ isoform that has a role in cutaneous scarring. Thus, the Examiner argues that it would have been obvious to one of ordinary skill in the art at the time of the invention to make nucleic acid ligands in order to target TGFβ2 and to use these ligands to inhibit a TGFβ2 in cells in vitro. Further, the Examiner asserts that it would have been obvious to one of ordinary skill to conjugate the ligands to a

solubility modifying moiety such as PEG as taught by Tullis in order to improve cellular uptake. Further,

> One of ordinary skill in the art would have had a reasonable expectation of success in making a conjugate of solubility modifying moiety and a nucleic acid ligand because Tullis teaches that such oligonucleotide conjugates can be made using routine synthesis methods. Thus claims 1 and 3-5 would have been obvious, as a whole, at the time of invention.

Office Action at 7.

Applicants respectfully disagree. In the present invention Claim 1 teaches a method of inhibiting TGFβ2 comprising contacting said TGFβ2 with a nucleic acid ligand of TGFβ2. The prior art referenced by the Examiner (Shah et al.) teaches targeting TGFβ2 with an antibody with subtle success. The reference describes that depending on the antibody isoform, subcutaneous scarring is altered. Additionally, Gold et al. teaches a method of identifying nucleic acid ligands. The Examiner argues that these two prior art references render the present invention obvious. A nucleic acid ligand is not an antibody. The term nucleic acid ligand antibody has been used in order to delineate the mode of action of a nucleic acid ligand, versus the mode of action of a nucleic acid which is utilized as a therapeutic agent to target genomic DNA. However, the nucleic acid ligand is not an antibody. As such, predicting the ability of a nucleic acid ligand to target TGFβ2 is not obvious. However, if for the sake of argument, utilizing a nucleic acid ligand to target TGFβ2 was "obvious to try" (which is not the accepted standard) there is no reasonable expectation of success. The fact that an antibody interferes with TGFβ2 action, and in this case may affect scar tissue formation, does not predict success for an entirely different moiety, i.e., a nucleic acid ligand, which binds through a different mechanism. Binding in the present invention is through a nucleic acid/growth factor interaction whereas the exchange in Shah et al. describes an antibody/growth factor interaction. Accordingly, success for the instant invention cannot be predicted.

Further, the addition of PEG, as denoted in Claims 3 and 5, is not obvious in view of Tullis and Gold. The Tullis reference teaches novel nucleic acid conjugates for "inhibiting **intracellular** mRNA maturation . . .[c]onjugates comprise a relatively short oligonucleotide sequence, a linking group, and a group which modifies the HLB (hydrophilic lipophilic balance) to provide an amphiphilic product." *See* WO 88/09810, page 4, lines 1-8 (emphasis added).

Tullis teaches the use of nucleic acid conjugates in relation to **intracellular** events. Further, Tullis discloses, "the amphiphilic nature of the product [nucleic acid conjugate] aids in the transport of the conjugate across the cellular membrane, and can provide additional advantages, such as increasing aqueous or liquid solubility of nucleic acid derivatives, e.g., use of an amphiphilic group to enhance water solubility of long chain methyl phosponates and stabilizing normal nucleic acids to exonuclease digestion." *Id.*, at lines 9-15. Thus, Tullis is limited to conjugates having an increased ability to be transported across the cellular membrane, and to increase the water solubility and stability of the conjugate to exonuclease digestion.

As discussed above, nucleic acid ligands targeting a growth factor have an entirely different mode of action than nucleic acids targeting genomic DNA. The present invention is directed towards molecules having a non-intracellular target; TGFβ2. TGFβ2 is en extracellular moiety; the ability to cross the cellular membrane (as in the case of nucleic acids targeting genomic DNA) is not an issue. The present invention teaches the use of conjugates for modifications yielding a higher stability in serum and animals. The teachings of Tullis to utilize conjugates for enhanced membrane transport or stability with regard to exonuclease digestion is not applicable. Applicants submit that, as such, there is no prediction of success for the instant invention from the Gold *et al.* teachings of a method for identifying nucleic acid ligands by a process of *in vitro* selection and amplification and the Tullis teachings of nucleic acid conjugates comprising an antisense conjugated to a solubility modifying moiety that may be hydrophobic.

In light of the preceding arguments, Applicants assert that the present invention is not obvious in view of Gold et al., Tullis and Shah et al. Reconsideration is respectfully requested.

Closing Remarks

Applicants believe that the pending claims are in condition for allowance. If it would be helpful to obtain favorable consideration of this case, the Examiner is encouraged to call and discuss this case with the undersigned.

This constitutes a request for any needed extension of time and an authorization to charge all fees therefore to deposit account No. 19-5117, if not otherwise specifically requested. The

undersigned hereby authorizes the charge of any fees created by the filing of this document or any deficiency of fees submitted herewith to be charged to deposit account No. 19-5117.

Respectfully submitted,

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/Katherine Lobel-Rice/

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